

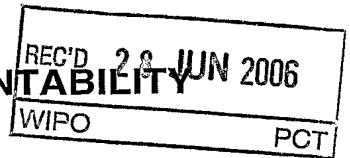
PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



| | | | |
|---|--|--|----------------------|
| Applicant's or agent's file reference P 67869 | FOR FURTHER ACTION | | See Form PCT/PEA/416 |
| International application No. PCT/EP2005/002389 | International filing date (day/month/year) 07.03.2005 | Priority date (day/month/year) 08.03.2004 | |
| International Patent Classification (IPC) or national classification and IPC INV. C07D495/04 | | | |
| Applicant KRKA, TOVARNA ZDRAVIL, D.D., NOVO MESTO | | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | | |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p> | | | |
| Date of submission of the demand 27.12.2005 | | Date of completion of this report 26.06.2006 | |
| Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 | | Authorized officer Diederen, J Telephone No. +31 70 340-1097 | |



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/002389

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-24 as originally filed

Claims, Numbers

1-32 as originally filed

Drawings, Sheets

1, 2 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/002389

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-32 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-32 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-32 |
| | No: Claims | |

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: WO 2004/006933 A (KRKA, D.D., NOVO MESTO; KOTAR JORDAN, BERTA; VRECER, FRANC; GRČMAN, MA) 22 January 2004 (2004-01-22) cited in the application

1. Novelty (Article 33(2) PCT)

The present application fulfills the requirements of Article 33(2) PCT with respect to Novelty.

The present application deals in claims 1-4 with a isopropanol/water solvate of olanzapine. Claims 5-22 pertain to a process for the preparation of a solvate according to claim 1 of the present application. Claims 23-25 pertain to processes and uses of a solvate according to claim 1 for the preparation of other solvates of olanzapine. Claims 26-32 pertain to a process for the preparation of form I of olanzapine, wherein a precursor of form (I) and form (I) is recrystallised from a liquid medium, which is present in a container containing at least one polymer.

Document D1, which is regarded the closest prior art document, discloses in example 8 an iso-propanol solvate of olanzapine (olanzapine / iso-propanol = 1 : ½). The compound claimed in claim 1 of the present application is a solvate of water and iso-propanol (olanzapine : water : iso-propanol = 1 : 1 : ½). Claim 1 and its dependent claims 2-4 are therefore also novel. Claims 5-22, claiming processes to prepare the novel solvate according to claim 1, are also novel. Claims 23-25 are therefore also novel over the prior art.

Claims 26-32 are novel as nowhere in the prior art, a process for the preparation of Form (I) of olanzapine is disclosed which is performed in a vessel comprising a polymer.

2. Inventive Step (Article 33(3) PCT)

The present application fulfills the requirements of Article 33(3) PCT with respect to

Inventive Step.

The closest prior art to claim 1 of the present application is document D1, which discloses an isopropanol solvate of olanzapine. The problem to be solved in D1, is the same problem as in the present application: i.e. the provision of an alternative solvate of olanzapine, for the preparation of Form (I) of olanzapine.

The difference of the subject-matter disclosed in the present application, as compared to the disclosure in D1 is that in the present application an iso-propanol/hydrate is claimed whereas in D1, an iso-propanol solvate is disclosed.

In D1 it is stated on page 4 last paragraph, that the use of hydrates as starting material for the preparation of Form (I) is undesirable, as this would lead to the formation of hydrates in the final product. It is said that the use of hydrates is not recommendable. This disclosure therefore teaches away from the subject-matter of the present application.

The problem to be solved by the applicant was to provide an alternative solvate for the preparation of Form (I) of olanzapine, without formation of hydrates. Starting from document D1, it would not be obvious that the hydrate of the present application would solve the latter problem. This result is unexpected as document D1 teaches away from the present application.

It is therefore considered, that the subject-matter of claims 1-25 is inventive over the prior art.

Claims 26-32 pertain to a process for the preparation of form (I) of olanzapine by crystallization or precipitation of a precursor in a vessel comprising at the surface at least one polymer. The advantage of using the polymeric surface is that a higher degree of purity of form (I) can be obtained by using a polymeric surface.

The problem to be solved was to provide an improved process for the preparation of Form (I) of olanzapine. Starting from D1, a skilled person would not expect, that by using a polymeric surface, the purity of the end product would be higher than without. This is an unexpected effect, which is not derivable from the prior art. It is therefore considered, that the subject-matter of claims 26-32 is inventive over the prior art.

Re Item VIII

Certain observations on the international application

The invention in claims 9-32 are disclosed in a manner insufficiently clear and complete to be carried out by a person skilled in the art (Article 5 PCT).

Claim 9 does not contain any features of how to perform the process. Claim 10 does not contain information how the isopropanol/water solvate is converted into the methylene chloride solvate. Claim 10 furthermore does not contain information how the dichloromethane solvate is converted into form (I). Step (b) of claim 10 is disclosed in a sufficient way in claim 17 of the present application.

Claims 23 and 24 does not contain any features which a skilled person would need to actually prepare other solvates or anhydrous forms of olanzapine.

The fact that the description gives details about how to perform the present invention, it is essential, with respect to Article 6 PCT, that the claims comprise all these essential features for carrying out the invention. These features should therefore be included in the claims.